

REMARKS

Claims 5, 9-16, 19-23, 26 and 30-38 are pending and under examination in the above-identified application. Claims 5, 26, 32 and 33 have been amended above. Support for the amendments can be found throughout the application. Specifically, support for the amendment can be found, for example, at page 6, lines 7-10, and lines 24-32, and at page 7, lines 7-13 of the application. New claims 39-64 have been added. Support for the new claims can be found in pending claims 5, 9-16, 19-23, 26 and 30-38 as well at, for example, page 19, lines 9-11. Further, claim 9 has been amended to correct an informality. Accordingly, the amendments do not raise an issue of previously presented matter and entry thereof is respectfully requested.

Corrected Drawings conforming to the requirements of 37 C.F.R. §1.84 for Figures 8-10 are submitted herewith under 37 C.F.R. §1.85 for substitution with current Figures 8-10. The corrected Drawings conform to those proposed by Applicants in their response dated November 8, 2002, and approved by the Examiner in the Office Action mailed September 23, 2003. Entry thereof is respectfully requested.

Applicant would like to thank Examiners Forman and Lu for extending a personal interview with Applicant's representatives on January 20, 2004. As recorded in the Interview Summary, the rejection under 35 U.S.C. § 102(e) was discussed. The amendments above and remarks below are believed by Applicant to substantially conform to the subject matter discussed in the interview and result in the Examiner's reconsideration of the rejection.

Claim 9 is objected to allegedly because of an informality. Because the objection is merely a semantic distinction, Applicant's have amended claim 9 to substituted the term "off said solid support" with the term "from said solid support." Accordingly, Applicants respectfully request withdrawal of this ground of objection.

Rejections Under 35 U.S.C. §102

Claims 5, 13 and 32 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Barany et al., U.S. Patent No. 6,027,889. The Office Action alleges that Barany et al. describe the detection of nucleic acid sequence differences using coupled ligase detection and polymerase

chain reaction (PCR). Pointing to Figures 12-17, the Office Action asserts that the first and second probes described by Barany et al. are considered to be the claimed first and second ligation probes and that the 5' upstream primer-specific portion in the first probe is considered to have two parts corresponding to an UUP and an adaptor sequence. The 3' downstream primer-specific portion in the second probe is asserted to be a DUP and that the hybridized adjacent probes are ligated together. The exonuclease I digestion step is alleged to correspond to the claimed step of removing non-hybridized probes while the mutant sequence shown in Figure 12 is asserted to be an interrogation position. Finally, amplification is asserted to occur by PCR and products captured by hybridization with an array of different capture oligonucleotides. The Office Action appears to specifically rely on the Barany et al. probes having adapters sequences because of its interpretation that the 5' upstream primer-specific portion has two parts, consisting of both an UUP and an adaptor.

The claims are directed to a method of determining the identification of a nucleotide at a detection position in a target sequence. The method includes hybridizing a first and second ligation probe to first and second target domains of a target sequence. The first ligation probe consists of a first portion containing an upstream universal priming site (UUP) and a second portion containing a first target specific sequence. The second ligation probe consists of a third portion containing a downstream universal priming site (DUP) and a fourth portion consisting of a second target specific sequence. Finally, at least one of the first or second ligation probes contains a fifth portion consisting of an adaptor sequence.

The Examiner appears to assert that the UUP portion or the DUP portion of the claimed probes can include both a UUP or a DUP and an adaptor portion. Applicants contend that this interpretation is unfounded, especially in light of the recitation of portions 1-5 in the ligation probes of the invention. The claims specify different elements within the probes and a correspondence to different portions within the probes. Accordingly, the claims cannot be anticipated by Barany et al..

A further distinction between Barany et al. and the claimed invention is that the purported adaptors described by Barany et al. appear to correspond to a region distinct from the adaptors of

the claimed probes. Briefly, the purported adaptors described by Barany et al. appear to correspond to a region within a target sequence. For example, the previous Office Action stated:

PCR products were hybridized with a DNA array with different capture oligonucleotides immobilized at different particular sites and had nucleotide sequences complementary to the unique nucleotide sequences across the ligation junctions of given probe sets.

Office Action mailed January 29, 2003, pages 4-5.

However, the adaptors within the claimed probes generally correspond to exogenous sequences. In this regard, the specification teaches at page 19, lines 9-11, that an adaptor sequence is distinct from a target sequence when it states “[a]n “adapter sequence” is a sequence, generally exogeneous [*sic*] to the target sequences, e.g. artificial, that is designed to be substantially complementary (and preferably perfectly complementary) to a capture probe on the array.” Because Barany et al. purportedly describes adaptors that correspond specifically to target sequences that correspond to “a nucleotide sequence across the ligation junction” and the claimed adaptors correspond to fifth portion of a probe differing from the second and fourth target specific sequence, the probe configuration of Barany et al. teaches away from the adaptors as currently claimed. Accordingly, Barany et al. cannot anticipate the claimed invention.

In light of the claims reciting that the probes contain first, third and fifth portions corresponding to a UUP, a DUP and an adaptor sequence, respectively, and in light of the description in the specification specifying that an adaptor sequence differs from the target sequence because it can be exogenous, Applicant’s contend that the claims cannot be anticipated by Barany et al.. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Rejections Under 35 U.S.C. §103

Claims 14-16 and 34 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Barany et al. in view to of Walt et al., U.S. Patent No. 6327,410. The office concedes that Barany et al. does not disclose the array as claimed in claims 14-16 and 34. Walt et al. is alleged to describe a fiber optic bundle with a patterned surface having discrete sites with subpopulations

of microspheres containing first and second capture probes as recited in claims 14-16 and 34. The Office alleges that in the absence of unexpected results one skilled in the art would have been motivated to combine the teachings of Barany et al. with Walt et al. because the replacement of one array type with another type would not change the steps of the experiment.

Claims 14-16 and 34 depend from independent claims 5, 26, 32 or 33. Although clear in the claims as previously pending, these independent claims now recite that the adaptor portion of a ligation probe corresponding to an adaptor sequence is distinct from either of the first through fourth portions of the claimed ligation probes. The rejection appears to be based on the Office's interpretation that the UUP or DUP can include an adaptor sequence. However, Applicants' have claimed distinct portions of the claimed ligation probes. These distinct portions are absent from the purported description in Barany et al. and the cited references neither provide a suggestion or motivation to identify a nucleotide at a detection position in a target sequence using a fifth portion consisting of an adaptor sequence. Absent such a suggestion or motivation, the claims cannot be obvious over the cited art.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 180 USPQ 580 (C.C.P.A. 1974); M.P.E.P. §2143.03.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness, at least because all the components of the claimed ligation probes are not taught or suggested by the cited art. The pending claims recite ligation probes containing a fifth portion, distinct from target-specific portions or UUP or DUP portions, or where the fifth portion corresponds to an exogenous sequence. However, the cited references, alone or in combination, at least do not teach or suggest a ligation probe containing these elements. For example, Barany et al. purports to describe an adaptor oligonucleotide that corresponds to a nucleotide sequence across the ligation junction. Because the ligation junction corresponds to a target-specific sequence, the purported description of Barany et al. do not teach or suggest an adaptor portion distinct from other portions as claimed. In the absence of a teaching or suggestion in the cited references of each of the components of the claimed ligation probes, the Office has not

established a *prima facie* case of obviousness of any of the claims under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Independent claims 26 and 33 and claims 10-13, 19-22, 31 and 35 depending therefrom stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Zhang et al, U.S. Patent No. 5,876,924, in view of Barany et al. The Office asserts that Zhang et al. describes two oligonucleotide probes, Capture/Amp-probe-1 and Amp-probe-2, hybridized adjacently on a target nucleic acid where probe-1 is biotinylated. Unbound reactants are separated using streptavidin-coated beads as an immobilized support, ligation of probes and amplification using PCR for detection of a single mutation. Probe-2 is asserted to have two parts corresponding to an UUP and an adaptor sequence. Barany et al. is further asserted to describe the use of an array and determining the nucleotide at the detection position as recited in steps (g) and (h) of claims 26 and 33. The Office alleges that one skilled in the art would have been motivated to combine the teachings of Zhang et al. with Barany et al. because the replacement of one ligation and amplification method with another method would not change the result. In maintaining this ground of rejection, the Office appears to rely on the assertion that since both the method of Zhang et al. and the claimed method include the common step of ligation chain reaction, that there is no change in the basic principle or design between the two methods.

As with the previous rejections over Barany et al. under §102 or Barany et al. in view of Walt under §103, the Office similarly contends that Zhang et al. describes a probe that contains both a UUP and an adaptor sequence. In this regard, the Office Actions states that the “domain of AMP-PROBE-2 is considered to have two parts: UUP and adaptor sequences” (emphasis added). However, Zhang et al. fails to describe an adapter sequence. Moreover, neither the current or the previous Office Action shows how the Amp-Probe-2 contains either or both a UUP and an adaptor sequence. Instead, Amp-Probe-2 shown in cited Figures 1 and 2 appear to illustrate a sequence that is either labeled or biotinylated for detection. There is no teaching or suggestion in Zhang et al. of separate sequence portions in the Amp-Probe-2 containing a DUP and adaptor sequence. In contrast, the claimed ligation probes claim first or

third portions containing a UUP or a DUP, respectively, and a fifth portion containing an adaptor sequence.

For the reasons set forth previously, neither Zhang et al. alone, or Zhang et al. in view of Barany et al., teach or suggest a first and second ligation probe having the five portions as claimed. Accordingly, the cited references fail to teach or suggest all the elements of the claimed invention and cannot provide a basis for a *prima facie* case of obviousness.

Further, there is similarly no motivation to combine the cited art references. As stated previously and acknowledged in the current Office Action, if the proposed modification or combination of the cited art would change the principle operation of the art being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). The Office Action appears to assert that the combination would not alter the principle operation allegedly because both have the common method step of directed to ligation chain reaction.

Applicants contend that reliance on a ligation step for support that the principle operation is unchanged fails to recognize a unobvious feature of the claimed method. The combination of the references would require substantial reconstruction and redesign of the elements shown in the primary reference to Zhang et al. as well as a change in the basic principle under which Zhang et al. was designed to operate. As stated previously, the ligation step of Barany et al. operates on amplified products whereas the ligation step of Zhang et al. operates on target sequences before amplification. Hybridization specificity required to detect an amplification product is different compared to the hybridization specificity required to detect a target sequence. As such, the ligation step performs different and separate functions in each method within the cited references.

In light of the above remarks, Applicants maintain that the cited references to Zhang et al. in view of Barany et al. fail to teach or suggest all the elements of the claims and fail to provide a motivation to combine. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 9, 23 and 30 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Zhang et al. in view of Barany et al., as applied above, and further in view of Seradyn Particle Technology. Seradyn Particle Technology is alleged to describe that streptavidin-coated paramagnetic beads of Zhang et al. consist of plastic material.

Claim 37 also stands rejected under 35 U.S.C. §103(a) as allegedly obvious over Zhang et al., in view of Barany et al., as applied above, and further in view of Monforte et al., U.S. Patent No. 5,830,655. Claim 36 stands rejected under 35 U.S.C. §103(a) over this combination of references and further in view of Brown et al., U.S. Patent No. 5,807,522. Claim 38 similarly stands rejected under 35 U.S.C. §103(a) over the combination of Zhang et al, in view of Barany et al. and Monforte et al. and further in view of Johnson et al.

With respect to claim 37, Monforte et al. is alleged to describe the immobilization of nucleic acid templates by attachment to a solid support before a primer extension assay. With respect to claim 36, Brown et al. is alleged to describe immobilization of nucleic acids onto a support consisting of charged groups. With respect to claim 38, Johnson et al. is alleged to describe photocrosslinking of a nucleic acid onto a solid support.

Claims 9, 23, 30, 36 and 37 all depend from one or more of the independent claims 5, 26, 32 and 33. Accordingly, the dependent claims contain all the limitations of the base claims from which they depend. As set fourth above, neither Barany et al. in view of Walt nor Zhang et al. in view of Barany et al. provide all the elements of the claimed invention or a motivation to combine the respective references. Accordingly, the independent claims are unobvious over the cited combination of references. The above tertiary references are cited allegedly for describing a further element found within the dependent claims. Because the cited art fails to describe each and every element of the claimed invention and because the tertiary references are directed to further elements within the dependent claims, the citations to Seradyn Particle Technology, Monforte et al. or Johnson et al. cannot cure the deficiencies of the primary and secondary references. Accordingly, the cited art to claims 9, 23, 30, 36 and 37 cannot teach or suggest each and every element of the claimed invention. Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

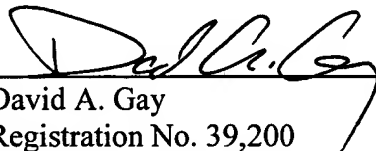
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CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

Respectfully submitted,

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